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Hyaluronic acid versus simple emollient for the management of radio-induced skin toxicity: results of an open-label, phase III trial

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Background: To avoid the late skin complications efficious treatment of the early radio-induced epithelitis is needed. The treatment of radio-induced early skin reactions is usually disappointing. Hyaluronic acid is one of the most recent topical products used in this indication, and providing interesting preliminary results.

Materials and Methods: Breast cancer patients with grade 1−2 radio-induced epithelitis during postoperative radiotherapy were eligible. They were randomised to receive either hyaluronic acid (A) or simple emollient (B). The primary endpoint was the clinical evaluation of the erythema (success *versus* failure). Secondary endpoints were the evaluation of skin colorimetry, pain, and quality of life.

Results: Two-hundred patients were enrolled (A = 99, B = 101). Seventy-three patients (36.5%) stopped prematurely the treatment without difference in the reason of treatment interruption. Ninety-five patients per treatment arm were evaluable. There were 23 failures (24.2%) in the hyaluronic acid arm, and 32 (33.7%) in the simple emollient arm (p = 0.15). Among risk factors of delay in healing, body mass index and size of epithelitis were independently associated with failure to local treatment. The relative reduction of colorimetric levels was 20.4% in hyaluronic acid group, and 13% in simple emollient group (p = 0.46). According to the quality of life assessment, there was a trend in a lower level of pain in patients receiving hyaluronic acid (p = 0.053).

Conclusion: The present study showed no significant difference between hyaluronic acid and simple emollient in the treatment of acute radio-induced epithelitis, even if there was a trend to an improvement in pain and skin colorimetry.

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A novel skin assessment tool for inflammatory breast cancer (IBC)

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Background: IBC is an aggressive carcinoma representing 1 to 6% of all invasive breast cancer. IBC has distinct clinical, pathological, and molecular features from other types of BC. IBC is characterized by a rapid onset of diffuse skin erythema and edema resulting in a pitted appearance (peau d'orange), tenderness, induration, and warmth of the involved breast. IBC is designated as non-measurable according to RECIST and there exists no standardized skin assessment tool. For this reason, the IBC Skin Assessment Tool (IBSAT) was created. The IBSAT incorporates the following disease manifestations: the presence and extent of plaques and nodules, grade of erythema, induration/Peau d'orange, and ulceration. Response criteria are based upon changes in size and/or grade of the disease manifestations.

Methods: The IBSAT was retrospectively applied to EGF103009, a phase II study of lapatinib in 153 pts with relapsed or refractory IBC [Kaufman 2009]. Three investigators independently assessed digital photos of 17 pts for all recorded timepoints (range: 2−12 months) and assigned a response of complete (CR), partial (PR), stable (SD), progressive (PD), or unknown. Unknown assessments were imputed as appropriate based on the assessments at previous and subsequent timepoints. In addition, timepoints following a PD assessment were treated as PD. PD concordance was calculated as the % of assessments in agreement with respect to PD and non-PD, both by pt and by time point. Pairwise PD concordance was calculated among the 3 investigators and between each of the 3 investigators vs. the independent review that was done as part of the EGF103009 study. Response concordance was calculated as the % of assessments in agreement with respect to response (CR/PR) and non-response by pt.

Results: PD concordance between pairs of investigators was good both by pt (71%, 71%, 88%) and by timepoint (86%, 79%, 90%). Similarly, PD concordance between each investigator and the independent reviewer was high by pt (94%, 88%, 63%) and by timepoint (85%, 77%, 77%). Response concordance was 94%, 94%, and 88% between pairs of investigators and 88%, 88%, and 81% between each investigator and the independent reviewer.

Conclusion: The IBSAT provides a reproducible means to assess cutaneous disease in IBC. This skin assessment tool is being prospectively applied in an ongoing phase III study in pts with recurrent Her2+ IBC.

References

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The clinical significance of the estrogen receptor beta expression for endocrine therapy in patients with estrogen receptor alpha-negative and progesterone receptor-positive breast carcinoma

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Background: Estrogen receptor (ER) is the key therapeutic target in breast cancer. ERβ has recently been identified to be distinct from ERα. In contrast to ERα, the functions of ERβ in breast cancer are still unclear. We sought to determine whether the expression of ERβ can be used as a predictive marker for endocrine therapy for patients with ERα-negative breast cancer.

Materials and Methods: Formalin-fixed, paraffin-embedded tumor specimens from 52 patients with ER-/PR+ invasive breast cancer were immunostained for their ERβ expression. These patients were treated with adjuvant tamoxifen. The results were correlated with various clinicopathological variables and the follow-up data. The expressions of p53 and HER-2/neu were also analyzed and correlated with the ERβ status.

Results: An ERβ expression was observed in 53.8% (28/52) of the breast cancer samples. There was no correlation between the ERβ expression and the other clinicopathologic factors (age, tumor size, histologic type, nodal status, histological grade, stage, therapeutic modality, progesterone receptor (PR) expression, p53 expression and HER-2/neu expression). Recurrence was present in 7.7% (2/26) of the patients whose tumors had an ERβ expression, as compared to the presence of recurrence in 36.4% (8/22) of the patients whose tumors had no ERβ expression ($p < 0.05$). The patients with ERβ negative-tumors revealed lower disease free survival rate than those with ERβ positive-tumors ($p < 0.05$). Of the 52 patients, 10 (19.2%) were p53 positive, and 11 (21.2%) were HER-2/neu positive. No significant correlations were observed between ERβ and p53 or HER-2/neu.

Conclusions: These results suggest that ERβ might be a predictive marker of a response to endocrine therapy in patients with ER-/PR+ invasive breast cancer, although this needs to be confirmed by additional studies.

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Histological assessment of ductal carcinoma in situ size in the absence of specimen slice radiology

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Background: Accurate assessment of size and adequacy of excision of Ductal Carcinoma in Situ (DCIS) can be challenging. We have no ready access to specimen radiology and therefore rely on widely sampling specimens with a pre-operative diagnosis of DCIS. While this may result in an increase in laboratory workload, we believe that this provides an accurate assessment of DCIS size and margins. We therefore performed this review of our DCIS cases to assess correlation of histological with mammographic size, and its relation to the need for re-excision.

Materials and Methods: All cases of DCIS from Breast Screening Program from 2004 to May 2008 were identified. The maximum dimension of DCIS was retrieved from the histology report and compared with the mammographic dimension. The slides were reviewed for cases with greater than 10 mm discrepancy.

Results: 62 cases of DCIS were identified. 28 (45% of the total 62) showed <10 mm difference between histological and mammographic size. 27 (44%) had a histological size >10 mm more than the mammographic size, while seven (11%) had a mammographic size >10 mm more than the histological size. As a first procedure 60 (97%) underwent wide

local excision and two (3%) mastectomy. Of those undergoing wide local excision seven (12%) subsequently underwent completion mastectomy and 10 (17%) re-excision. 14 (52%) of the cases in which histological size was >10 mm in excess of mammographic size required re-excision, compared with 2 (7%) of those showing <10 mm difference. Both of the two cases undergoing primary mastectomy had a histological size >10 mm in excess of mammographic size. Furthermore 14 (82%) of those requiring re-excision or completion mastectomy had a histological size >10 mm in excess of mammographic size. On review of slides, the discrepancy between histological and mammographic size appeared to be due to the presence of DCIS at the peripheries of the specimen that was not appreciated on radiological assessment because of the absence of microcalcification.

Conclusions: Our study demonstrates that there are discrepancies between histological and mammographic sizes and that such discrepancies result in an increased requirement for re-excision. It would appear that these discrepancies result because not all DCIS within a lesion is associated with microcalcification. We believe, therefore that, despite the extra workload, wide sampling and tumour mapping may be superior to specimen radiology alone.

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Contribution of cytological CSF analysis to the management of patients with breast cancer; a retrospective analysis over two decades

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Background: Metastatic spread of breast cancer to the central nervous system (CNS) is relatively frequent. Unequivocal diagnosis of such spread may be difficult as the neurological and radiological presentation are very diverse. Since long, cytological examination of the cerebrospinal fluid (CSF) is considered as a valuable, additional tool to prove the diagnosis of CNS metastasis of breast cancer. However, the exact value of CSF cytological examination for patient management is not clear.

Aim: To assess the contribution of cytological CSF analysis to the management of breast cancer patients.

Materials and Methods: In a single pathology department serving two breast cancer centre hospitals we retrieved information of all patients (n = 81) with a histological diagnosis of breast cancer that had at least one lumbar puncture in the period of Oct. 1989 to Oct. 2009 to allow for cytological CSF examination. Relevant information was retrieved from the clinical (esp. type and stage of breast cancer, neurological signs and symptoms) and radiological records. For cytological CSF analysis, a cytospin procedure was performed, the slides were Papanicolaou stained. The cytological diagnosis on CSF was classified in the categories proposed by the 1996 NCI-sponsored conference approach: malignant, suspicious for malignancy, atypical, benign and unsatisfactory.

Results: In 20 years 145 CSF examinations were performed in 81 breast cancer patients with a very diverse clinical and radiological context. Relatively frequent reasons to perform CSF examination were headache (n = 23), and spine or radicular pain (n = 12), in somewhat less than half of these patients malignant cells were detected in the CSF. A substantial number of patients without abnormalities on MRI (n = 20) and CT scans (n = 22) did have malignant cells in their CSF specimens (4 and 6, resp.). Repeated examination of CSF was performed in 37 patients (2−13 times) resulted in a change in cytological diagnosis from suspicious to malignant in only one patient.

Conclusion: This study underscores that cytological examination of the CSF is a very valuable tool for unequivocal diagnosis of metastatic spread to the CNS in breast cancer patients. Even in a substantial number of breast cancer patients with neurological symptoms but without radiological abnormalities on MRI and/or CT scans malignant cells are found in the CSF. In this study, the additional value of repeated cytological examination of CSF was very limited.

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Ki67 proliferation as a biomarker in neo-adjuvant breast cancer studies − core biopsy versus surgical sample

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Background: Proliferation is a key feature of tumor progression and is widely estimated by the assessment of the antigen Ki67 immunohistochemically. Ki67 is not only used as a static marker of proliferation, but also used as a marker of treatment efficacy. In neo-adjuvant breast cancer studies pre-treatment Ki67-index is assessed on material from either fine needle or core biopsies and compared with post-treatment Ki67-index in surgical samples. However, verification of the validity of Ki67 use to evaluate a treatment has not been previously studied. The aim of this study was to identify a potential baseline difference in Ki67-index between core biopsies and surgical samples in an untreated cohort.

Material and Methods: Tumor tissue from core biopsies and surgical samples from a retrospective consecutive cohort of 50 women operated for breast cancer was collected. The core biopsies and the corresponding operation samples were evaluated for proliferation through immunohistostaining of Ki67 using the MIB-1 antibody. Ki67 was examined on 2x, 10x and 40x magnification to identify hotspots, areas with increased number of Ki67 positive tumor cells. Using 40x magnification over the hotspot, 10 cancer cells at a time were counted covering the entire field of magnification or until 1000 cancer cells were evaluated. Each core biopsy and operation sample was evaluated twice with the counter blinded to the relationship between samples.

Results: Since no treatment was given during the intervening time between biopsy and operation, no significant difference in proliferation values was expected. However, preliminary results show that the proliferation in the biopsy samples was slightly (2%), but significantly (p = 0.04), higher than proliferation in the operation samples. In dichotomized analyses using the clinically used cut-off at 20% positive cells no significant difference between biopsy and operation sample was found. Statistical analyses further indicated that the number of cells needed to count in order to estimate proliferation index was 200 cells.

Conclusion: This study demonstrates a baseline decrease in proliferation index between core biopsy and operation samples, which needs to be taken into account when evaluating treatment efficacy in neo-adjuvant studies.

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Morphological and immunophenotypic analysis of triple negative breast carcinomas

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Background: Triple-negative breast cancer (estrogen receptor-negative, progesterone receptor-negative, and HER2-negative) is an aggressive disease without tumour-specific treatment options. Frequently they are associated with a basal phenotype. In the present study, we have analyzed the expression of basal markers and morphological characteristics in the triple negative breast carcinomas.

Method: A total of 117 consecutive cases of invasive ductal breast carcinomas diagnosed in our institution were screened for the triple-negative phenotype, and were subsequently evaluated for cytokeratins (CK): 5/6 and 17, p63, and c-kit immunoexpression. In addition, haematoxylin and eosin-stained sections of these tumours were studied for several morphological parameters such as appearance of tumour margin, the presence of lymphoid stromal infiltrate, comedo-type necrosis, and prominent central necrosis/fibrosis. The findings were correlated with patient and tumour characteristics.

Results: Triple negative breast carcinoma phenotype was found in 13.68% (16/117) in our series. Expression of CK5/6 showed 26 tumours (22.22%) and 35 (29.91%) were CK17-positive. Thirteen (11%) cases expressed c-kit, and sixteen (15%) showed p63 positive expression. A total of 11 (69%) triple negative tumours showed a CK5/6-positive expression, and 14 (87%) triple negative tumours expressed CK17 (p = 0.000). The triple negative cancers were different from the non-triple-negative carcinomas by having a high histological grade (75% versus 15%, p = 0.000), tumour size larger than 2 cm (49% versus 33% p = 0.06), and by pushing border (62% versus 10%, p = 0.000). No differences were seen for the presence of lymphoid stoma infiltrate, comedo-type necrosis, and prominent central necrosis/fibrosis. Also, c-kit expression was significantly higher in triple negative group than in non-triple negative group (p = 0.003), but no significant differences were found between triple negative and non-triple negative cancer group in relation to p63 expression.

Conclusions: Triple negative breast cancers differ from non-triple negative breast cancers in several aspects, and have a higher malignant phenotype. The majority, but not all, of the triple-negative breast carcinomas exhibit a basal-like phenotype. Thus, triple-negative should not be used as a surrogate marker for basal-like cancers. C-kit expression is more often present in the triple-negative tumour group than in non-triple negative cases. This data suggests that c-kit expression might be important as a potential target for molecular therapy in triple-negative breast cancer.